Type 2 diabetes, high-intensity training (HIT) and technology-support for home-based HIT

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TYPE 2 DIABETES, HIGH-INTENSITY TRAINING (HIT) AND TECHNOLOGY-SUPPORT FOR HOME-BASED HIT

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Resumé

This PhD project is based on problem-based research and takes its origin in the high incidence of type 2 diabetes and the profound impact this disease has on the quality of life of those who suffer from it as well as the societal costs attributable to this disease. The main ambition of my PhD project is to elucidate the therapeutic potential of physical training as an adjunct to dietary and pharmaceutical management to increase insulin sensitivity and control blood glucose. More specifically, the PhD project focuses on the use of high-intensity training (HIT), self-monitoring and use of technology for supervision.

The PhD project presents a new approach to diabetes treatment in the form of technology-based, supervised home-training using a timesaving HIT protocol. Furthermore, this PhD project studies the potential of using simple self-monitoring methods for measuring improvements in diabetes-related outcomes. A secondary aim was to elucidate if health literacy and attitudes towards diabetes affect home-training adherence. Two main research questions were raised:

- Which tendencies are detected in the association between HIT and diabetes-related outcomes measured with the use of simple self-monitoring methods (Question 1)?

- Is a home-based HIT protocol with technology-based supervision for patients with T2D feasible related to intensity and frequency of training, and do health literacy and attitudes towards diabetes affect adherence to HIT (Question 2)?

To answer these questions, four studies were conducted of which Study 1, 2 and 4 are classic hypothesis-driven studies, and Study 3 is a problem-driven study.

1. The use of self-monitoring methods in a HIT study on patients with type 2 diabetes: A pilot study.

The aim of this pilot study was to test the feasibility of a study protocol in patients with type 2 diabetes (T2D) and to obtain preliminary results of using simple self-monitoring methods for measuring diabetes-related changes after a period of HIT.

2. A self-monitoring approach for evaluating the effect of 3 weeks of HIT in type 2 diabetics. An intervention study.

The aim of this study was to study if the effect of a short period of HIT could be measured using simple methods that patients with T2D could easily learn to use and interpret by themselves. Furthermore, the study aimed at investigating these patients' compliance with HIT recommendations.

3. Translation and adaption of the Diabetes Attitude Scale (DAS) for use in patients with type 2 diabetes in Denmark. A pilot study.

This study was driven by the wish to use the Diabetes Attitude Scale (DAS) in Study 4 to measure attitudes towards diabetes in participating patients as previous studies have detected a correlation between a positive attitude and treatment adherence. However, the DAS was not available in a Danish version. Therefore, the task of this study was to translate and adapt the DAS for use in patients with T2D in a Danish population.

4. Evaluating a HIT-based home-training with technology-based supervision. A mixed-method study.

The aim of the study was to evaluate the combination of HIT-based home-training and technology-based supervision in patients with T2D with a particular focus on evaluation of training frequency and intensity, technology used for supervision, and any correlation between attitudes towards diabetes, health literacy and training adherence.

Based on the results from this PhD project, it appears possible to use simple methods to measure training-induced effect on diabetes-related parameters after a period of HIT. Furthermore, it appears that patients are able to reach both the right intensity in a HIT-based protocol as well as frequency of training only with the use of technology-supported supervision. Both the adequate health literacy and the positive diabetes attitude in patients included could help explain their high adherence.

Dansk resume

Introduktion: Dette Ph.d.-projekt er baseret på problem-baseret forskning og tager udgangspunkt i den høje forekomst af type 2 diabetes (T2D) og dens store indflydelse på livskvalitet hos patienter med T2D såvel som de samfundsmæssige omkostninger, som skyldes denne sygdom. Den primære ambition med Ph.d.-projektet er at belyse det terapeutiske potentiale af fysisk træning som et tillæg til behandling med kost og medicin for at øge insulinfølsomheden og kontrollen af blodsukker. Mere specifikt fokuserer Ph.d.-projektet på højintens træning (HIT), selvmonitorering samt brug af teknologi i supervision.

Formål: Dette Ph.d.-projekt præsenterer en ny tilgang til behandling af diabetes i form af teknologibaseret, superviseret hjemmetræning med brug af en tidsbesparende HIT-protokol. Derudover undersøger Ph.d.-projektet potentialet af brug af simple selvmonitoreringsmetoder til at måle forbedringer i diabetesrelaterede parametre. Et sekundært formål var at belyse, om health literacy og diabetes attitude kunne påvirke overholdelse af hjemmetræningen. To hovedspørgsmål blev adresseret:

- Hvilke tendenser er påvist i forbindelse med HIT og diabetesrelaterede resultater med brug af simple selvmonitoreringsmetoder (Spørgsmål 1)
- Er en hjemmebaseret HIT-protokol med teknologibaseret supervision for patienter med T2D mulig og påvirker health literacy og diabetes-attitude overholdelsen af HIT (Spørgsmål 2)?

Fire studier blev gennemført for at svare på disse spørgsmål. Studie 1, 2 og 4 er klassiske hypotesedrevne studier, mens studie 3 er problemdrevet.

Studie 1: Formålet med dette pilotprojekt var at teste gennemførligheden af en studieprotokol hos patienter med T2D samt at indsamle præliminære resultater af brug af simple selvmonitoreringsmetoder til at måle diabetesrelaterede ændringer efter en periode med HIT.

Studie 2: I dette studie var formålet at undersøge, om effekten af en kort periode med HIT kunne måles med brug af simple metoder, som patienter med T2D nemt kan lære at bruge og tolke selv. Derudover ville studiet undersøge disse patienters compliance med HIT.

Studie 3: Dette studie var drevet af ønsket om at bruge Diabetes Attitude Scale (DAS) i studie 4 til at måle attitude over for diabetes i deltagende patienter. Tidligere studier har fundet en sammenhæng mellem en positiv attitude og overholdelse af behandling. Udfordringen var, at DAS ikke eksisterede i en dansk version. Derfor var opgaven i dette studie at oversætte og tilpasse DAS til brug til patienter med T2D i den danske population.

Studie 4: Formålet med dette studie var at evaluere kombinationen af HIT-baseret hjemmetræning og teknologibaseret supervision hos patienter med T2D. Et særligt fokus var på at evaluere træningsfrekvens og intensitet, teknologien brugt til supervision samt sammenhængen mellem diabetes attitude, health literacy samt overholdelse af træningen.

Konklusion: Baseret på resultater fra dette Ph.d.-projekt synes det muligt at bruge simple metoder til at måle træningsinduceret effekter på diabetesrelaterede parametre efter en periode med HIT. Derudover tyder det på, at patienter kan opnå både den rette intensitet og frekvens i en HIT-baseret protokol kun med brug af teknologibaseret supervision. Både den tilstrækkelige health literacy og den positive diabetes-attitude hos patienterne kunne være en del af forklaringen på patienternes overholdelse af træningsprotokollen.

Acknowledgements

Approaching the time of submission of the PhD project has made me think of the journey this has been. This journey would not have been possible on my own. Therefore, I wish to express my gratitude to those who have contributed to this thesis coming to life.

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Preface

My interest in T2D and training began in 2005, when I was completing my Master's degree in Science (cand. scient) in Exercise and Sport Sciences from Copenhagen University. In my Master thesis, I had the opportunity to study the effect of strength training and endurance training on patients with type 2 diabetes. The beneficial effects from training on type 2 diabetes were intriguing to me and led me to follow this field of science in the following years.

My employment as a lecturer at the Department of Physiotherapy, University College of Northern Jutland, Denmark, furthered my interest in this field, as I began to lecture students about the effects of training on type 2 diabetes. In this context, I discovered research studying the effect of high-intensity training on type 2 diabetes, and based on the promising effects from this research, my motivation to explore this field began. My motivation was also driven by observing the challenge of increasing adherence to training in patients with type 2 diabetes and of the potential of incorporating technology in this aspect.

In 2013, I was enrolled as a PhD fellow at the Department of Health Science and technology, Aalborg University, Denmark. Since my enrolment, I have completed four studies with the aim of exploring the potential of using high-intensity training and technology in a rehabilitation approach for patients with type 2 diabetes.

The PhD thesis is based on the four studies I have conducted, unless otherwise stated. The PhD thesis consists of 8 chapters, and a brief overview of the thesis will be given in the next section.

Overview of the thesis

1. Introduction.
   This section includes an overview of T2D in relation to epidemiology, aetiology, pathology and pathophysiology. Furthermore, a brief description is given of the complications, along with how the disease is diagnosed and generally treated.

2. Physical activity and training
   The effect of physical activity and training on blood glucose and insulin sensitivity will be outlined as will the effect of physical training on oxidative stress and inflammation. As this PhD project focuses on HIT, special attention will be devoted to discussing the effect of this approach to physical training.

3. Setting
   In this section, a description of the setting of the PhD project is given. This includes a description of the diabetes rehabilitation offer provided by Aalborg Municipality where the present project is set. In addition, the research questions for this PhD project will be presented.

4. Technology
   Technology is another focus in this PhD project. First, definitions of technology will be described. Second, the use of technology in monitoring of diabetes-related outcomes will be covered. Third, the technology used in relation to physical activity will be presented. Fourth, a presentation of adherence and the components involved in adherence will be given. Finally, a description of how technology can affect adherence is presented.

5. Aims and overview
   This section will describe the aim of the PhD study and give an overview of the studies performed to answer the research questions posed.

6. Summary of studies
   This section includes a summary of the studies conducted in this PhD project. This also include a revisited section of Paper 2, which has been published.

7. Key results
   A brief presentation of the key results from the studies will be presented in this section

8. Discussion

The discussion will start out presenting and interpreting the main results; this will be followed by a discussion of methodological considerations in relation to trial design, patient recruitment, selection of simple methods, the use of interviews and the analysis of the interviews conducted.

9. Conclusions and perspectives
   A final chapter will present the conclusions of the PhD study and suggest perspectives and future research.

Definitions and abbreviations

Definitions:

Physical activity:	The term refers to "*any bodily movement produced by skeletal muscles that requires energy expenditure"* (1)
Training/physical training:	In this thesis, the terms "training" and "physical training" cover both the definition of physical training: *"The systematic use of exercises to promote bodily fitness and strength"*(2) and the definition of exercise: *"Activity requiring physical effort, carried out to sustain or improve health and fitness."* (3)
Hyperglycaemia:	Hyperglycaemia occurs when glucose is unable to enter the cell from the bloodstream
HbA_{1c}:	Glycated haemoglobin refers to the amount of haemoglobin (percentage or mmol/mol) to which glucose is irreversibly attached, and reflects the average glucose level in the previous 8-12 weeks (4)
Self-management:	The term refers to "*the taking of responsibility for one's own behaviour and well-being*" (5)
Self-monitoring:	Monitoring of health-related measurements by the patients themselves
High-intensity training:	In this PhD project, the term high-intensity training (HIT) is considered synonymous with high-intensity interval training (HIIT) and include training related to aerobic training using high intensity training in intervals

Abbreviations:

ADA:	American Diabetes Association
ADQ:	Adherence in Diabetes Questionnaire
AMP:	Adenosine monophosphate

ATP:	Adenosine triphosphate
BMI:	Body Mass Index
COPD:	Chronic obstructive pulmonary disease
CRP:	C-reactive protein
CVD:	Cardiovascular disease
DAS:	Diabetes Attitudes Scale
DIAB-Q:	Diabetes Intention, Attitude and Behaviour Questionnaire (DIAB-Q)
DSQM:	Diabetes Self-management Questionnaire
DXA:	Dual energy x-ray absorptiometry
EASD:	European Association for the Study of Diabetes
GP:	General practitioner
HbA_{1c}:	Glycated haemoglobin
HBM:	Health belief model
HIT:	High-intensity training
HR:	Heart rate
HOMA-IR:	Homeostatic model assessment of insulin resistance
$HR_{max:}$	Maximum heart rate
IDF:	International Diabetes Federation
IGT:	Impaired glucose tolerance
IL-6:	Interleukin-6
OGTT:	Oral glucose tolerance test

PAID:	Problem Areas in Diabetes
RCT:	Randomised controlled study
ROS:	Reactive oxygen species
SCT:	Systematic text condensation
SMBG:	Self-monitoring blood glucose
T1D:	Type 1 diabetes
T2D:	Type 2 diabetes
TNF-α:	Tumour necrosis factor-α
TOFHLA:	Functional Health Literacy in Adults
VO_{2max}:	Maximum rate of oxygen consumption

Table of content

1.Introduction

1.1 Epidemiology

The prevalence of type 2 diabetes (T2D) is growing around the world. The number of people with diabetes was approximately 425 million in 2017, with T2D accounting for approximately 90% of all cases (6,7). This number is estimated to have grown to 629 million worldwide by 2045 (6). In Denmark, the incidence of T2D was 138,400 in 2007; a number that had grown to 235,175 in 2017, which corresponds to a 58.85% increase according to the Danish Health Register (8). The main driver of the T2D epidemic is a growth in the number of people suffering from overweight and obesity (9).

T2D profoundly affects individuals who suffer from the disease, and vast societal costs are attributable to this disease. Individuals with T2D diagnosis face serious comorbidity, including stroke, kidney diseases, blindness and neuropathies (6). Moreover, studies indicate that there is an association between T2D and depression (10). At the socioeconomic level, healthcare costs that accrue to a patient with diabetes are approximately twice the costs of a person without diabetes, with costs growing with the burden of complications becoming heavier (11).

1.2 Aetiology

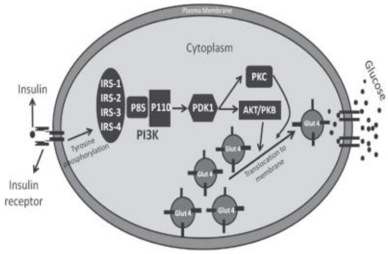
A number of factors like heredity, lifestyle, socioeconomic status and environment are all linked to the prevalence of T2D. If a relative suffers from T2D, the risk of being diagnosed with the disease is increased, and the risk is further increased if both parents suffer from T2D (12,13). Gestational diabetes during pregnancy is also associated with a higher incidence of T2D later in life (14). Lifestyle also plays a strong role in the development of T2D. An unhealthy lifestyle due to a hypercaloric diet and physical inactivity can lead to elevated body weight, increased waist circumference, dyslipidaemia, hyperglycaemia and insulin resistance, which may, in turn, lead to T2D (7). Because of the link between the risk of developing T2D and lifestyle, T2D is often referred to as a lifestyle disease. The relationship between socioeconomic status and T2D is well-established. Hence, low socioeconomic status and low level of education further unhealthy lifestyle, which increases the risk of T2D and this partly explains the difference in the prevalence of T2D (15). Furthermore, the time of diagnosis and the risk of complications are influenced by socioeconomic position, resulting in a later diagnosis and a higher risk of complications in persons with a low socioeconomic position than in persons with a better socioeconomic position (16). Finally, different elements of the environment are associated with the development of T2D.

Thus, factors such as walkability, green spaces and air and noise pollution have been connected to the risk of T2D (17).

1.3 Pathology and pathophysiology

Hyperglycaemia is a physiological state with a higher than normal concentration of glucose in the blood. Hyperglycaemia is the most common characteristic of pre-diabetes and manifest T2D (18). In T2D, hyperglycaemia is mainly caused by cellular insulin resistance, decreased insulin secretion and post-absorptive increased hepatic glucose secretion (7,13,19,20). Insulin resistance can be present without a diagnosis of T2D as long as insulin secretion provides sufficient insulin to counterbalance the insulin resistance (7).

In normal cells, glucose enters the cell either through insulin-dependent or non-insulin-dependent glucose uptake as illustrated in Figure 1. Insulin-dependent glucose uptake refers to a process whereby insulin binds to cell receptors, leading to a cascade of reactions resulting in translocation of glucose transporters into the cell membrane whereby glucose is allowed to enter the cell from the bloodstream (7,21). Non-insulin-dependent glucose uptake refers to glucose uptake initiated by an increase in the adenosine monophosphate (AMP): adenosine triphosphate (ATP) ratio resulting from muscle contractions (21). This leads to translocation of glucose transporters through a different pathway than the insulin-dependent pathway (21).



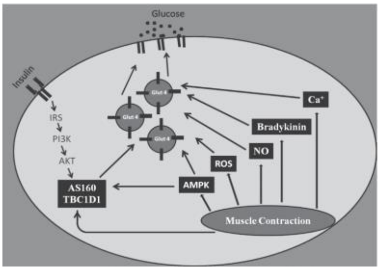


Figure 1: GLUT4 translocation stimulated by insulin and muscle contraction (21).

In patients with T2D, the insulin-dependent glucose uptake is affected due to insulin resistance (7). Insulin resistance results from a defect in the cascade of reactions that occur when insulin binds to cell receptors (7,13). This leads to a decrease in translocation of glucose transporters and thereby decreasing cellular glucose uptake, which contributes to hyperglycaemia (7). In addition, an increased hepatic glucose secretion aggravates hyperglycaemia (20). A dysfunction in the pancreatic insulin-producing β-cell due to chronic low-grade inflammation and oxidative stress will result in insulin deficiency at an early state in the development of T2D (19), causing an inadequate insulin concentration to counterbalance the insulin resistance (7,13). Therefore, β-cell dysfunction has been showed to be an important factor in development of T2D (19). As muscle cells are the primary site of peripheral tissue glucose uptake after a meal, insulin resistance in muscle cells profoundly impacts hyperglycaemia and T2D development (22).

β-cell dysfunction and T2D have been related to both low-grade inflammation and oxidative stress (19). These conditions are linked to inactivity, overeating and obesity, and they contribute to deterioration of insulin resistance (19). Oxidative stress is defined as an imbalance between reactive oxygen species (ROS) and the antioxidant defence (23). This imbalance can result in tissue damage. Both insulin resistance and pancreatic β-cell dysfunction are affected by oxidative stress, which affects the insulin-receptor-substrate (IRS) complex in the insulin-signalling cascade thereby impairing the effect of insulin (19). Furthermore, β-cells are low in antioxidant effect, resulting in cell damage and finally insulin deficiency. Overweight caused by overeating as well as inactivity also result in excess adipose tissue (24). Adipose tissue secretes non-esterified fatty acids, glycerol, hormones and pro-inflammatory cytokines to the bloodstream (25). Tumour necrosis factor-α (TNF-α) and C-reactive protein (CRP) are well-studied examples of pro-inflammatory cytokines leading to low-grade inflammation. TNF-α is thought to be involved in the development of insulin resistance (19,26), and CRP is a predictor of incident cardiovascular disease (CVD) (27). This leads to the contention that inflammation is implicated in endothelial dysfunction, atherosclerosis and CVD (19,28). Visceral adipocytes in particular contribute to inflammation, as they appear to be particularly potent in releasing pro-inflammatory cytokines (19).

1.4 Complications

Poorly treated T2D can lead to microvascular complications such as retinopathy, neuropathy, renal dysfunction and foot ulcers (29). Hence, a Danish study found that one-third of patients with T2D already suffer from complications at the time of diagnosis (30). Furthermore, the risk of CVD is doubled in patients with T2D (31,32), and CVD is the foremost cause of both morbidity and mortality (33). The risk of microvascular complications seems to be related to hyperglycaemia, and every 1% decrement in glycosylated haemoglobin (HbA1c) reduces the risk of these microvascular complications by 25-35% (34). The increased risk of CVD in patients with T2D is more related to traditional CVD risk factors than to T2D (30,31). These risk factors include obesity, dyslipidaemia and hypertension, among others (31), and are commonly seen in patients with T2D (35). Moreover, insulin resistance has been linked to the development of CVD, and low-grade inflammation associated with T2D is a possible contributor to atherosclerosis (34). This explains the high incidence and mortality rate caused by CVD in patients with T2D.

1.5 Diagnostics

Hyperglycaemia is the most important measure in diagnosing T2D (18), which may be diagnosed in several ways – all based on plasma glucose concentration. These methods include measuring fasting glucose level, 2-hour plasma glucose and HbA_{1c}. As can been seen in Table 1, the criterion for diagnosing diabetes from fasting glucose level is a glucose concentration exceeding 7.0 mmol/L after at least 8 hours of fasting and/or a plasma glucose concentration above 11.1 mmol/L 2 hour after an oral glucose tolerance test (OGTT). Diabetes is also diagnosed if HbA_{1c} exceeds 6.5% (18). (Classification and diagnosis of diabetes).

Table 1: Criteria for the diagnosis of diabetes

HbA1c ≥ 6.5%. The test should be performed in a laboratory using a method that is NGSP-certified and standardised to the DCCT assay *
OR
FPG ≥ 126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h. *
OR
2-h PG ≥ 200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water. *
OR
In a patient with classic symptoms of hyperglycaemia or hyperglycaemic crisis, a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L).

*In the absence of unequivocal hyperglycaemia, results should be confirmed by repeat testing. NGSP: National Glycohaemoglobin Standardization Program; DCCT: Diabetes Control and Complications Trial; FPG: Fasting plasma glucose; PG: Plasma glucose (18)

1.6 Treatment of type 2 diabetes

The three main components in treating T2D include dietary therapy, medicines and physical training, all of which aim to increase insulin sensitivity and improve blood glucose control. In order to choose the right treatment, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommend that: "*Providers and health care systems should prioritize the delivery of patient-centered care"* (36).

1.6.1 Dietary therapy

Being overweight and obese is associated with an increased risk of developing T2D and predicts disease progression (9). The ADA therefore recommends a minimum of 5-10% weight loss for overweight and obese individuals diagnosed with or at risk of developing T2D (37). Therefore, dietary therapy primarily aims to lower body weight by creating a caloric deficit while ensuring that guidelines for a healthy diet are met. Dietary therapy plays a role at three levels: primary prevention of T2D development, secondary prevention to further disease management and tertiary prevention to prevent disease progression (37,38). According to the ADA, no optimal ration of carbohydrates, protein and fat exists for patients with T2D (37). Instead focus should be directed towards increasing adherence by tailoring the dietary therapy and taking personal food preferences into account (37,38). Lowering body weight is associated with improved insulin sensitivity and glucose control (38). Furthermore, studies show that dietary measures have a positive effect on plasma lipids and lipoproteins (39) and glucose control (40) in patients with newly diagnosed T2D.

1.6.2 Medicine

Medicine used in T2D treatment serves different purposes. Some medicines aim at increasing insulin sensitivity in cells; others increase the function of pancreatic insulin-producing α-cells. A brief overview of some of the most commonly used drugs will be presented:

- Metformin is the most commonly used drug to improve blood glucose control as metformin reduces glucose release from the liver and, in addition, increases skeletal muscle glucose uptake (41,42).
- Sulfunylurea and glinidin stimulate the pancreas to produce more insulin (42).
- Thiazolidinediones increase the effect of insulin on fat and muscle tissue (42).
- GLP-1 analogues and DPP-IV-inhibitors increase insulin secretion and decrease pancreatic glucagon secretion (42).
- SGLT-inhibitors affect the kidneys to secrete more glucose in the urine (42).

The different types of drugs can be combined to obtain a better result. Furthermore, insulin can be injected when β -cell deterioration results in chronic lack of insulin and can be given in combination with the above-mentioned drugs. To sum up, drugs used in treatment focus on lowering the blood glucose concentration.

1.6.3 Physical activity and training

Physical training as a strategy for countering T2D has well-established effects, which are seen both after an acute bout of training and after a period of regular training (43–46). Physical activity and training have multiple positive effects on T2D in relation to disease pathophysiology and development of complications. As for the pathophysiology of T2D, participating in physical activity and training promotes glucose control because of increased cellular glucose uptake via the non-insulin-dependent pathway (43). This increased glucose uptake is active for hours after a single training session and contributes to preventing hyperglycaemia (46,47). Furthermore, regular physical training decreases HbA1c, hence improving glycaemic control, and thereby decreasing the risk of complications (44). Being physically active also lowers low-grade inflammation and oxidative stress related to T2D (48). The focus of the present PhD project is on physical activity and training. Therefore, a more thorough exposition of the positive effects will be presented in the following section.

2. Physical activity and training

As mentioned before, physical activity and training appear to be efficient in both preventing and treating T2D (28,45,49,50). Indeed, physical activity is highly efficient in preventing T2D. Hence, numerous studies have established a connection between being physically active and the incidence of T2D. The Finnish Diabetes Prevention Study discovered a lower T2D incidence following a lifestyle intervention with a mean duration of 3.2 years focused on diet and physical activity in 522 subjects with impaired glucose tolerance (IGT) (11%, 95% confidence interval (CI) 6-15% vs. 23%, 95% CI 17-29% in the control group) (51,52). These findings were supported by a review by Aune et al. (2015), who concluded that physical activity lowers the risk of developing T2D from 15-55% depending on the type of physical activity (53). The US Diabetes Prevention Program also found a lower incidence of T2D with a lifestyle intervention (58%, 95% CI 48-66%), and the decrease in incidence with a lifestyle intervention was lower than that accomplished with drug treatment (31% reduction, 95% CI 17-43%) compared with placebo (54). However, it is worth mentioning that the lifestyle intervention programs included both physical activity and diet. Still, even when only physical activity is studied, as in the study by Aune et al (2015), the incidence was lower (53). Moreover, it appears as if the sustainability of a prevention program is more important than the time of onset of the program (55). That said, Toumiletho & Schwarz (2016) also emphasize that early intervention is preferable in any prevention (55).

Physical activity and training also have positive effects on the treatment of T2D in relation to blood glucose control, insulin sensitivity, oxidative stress and inflammation. These positive effects have been established by several reviews and meta-analyses based on extensive research and will be presented in more detail in the following sections. Special attention will be given to the effect of HIT in the last section.

2.1 Blood glucose control and insulin sensitivity

A review by Way et al. (2016) concluded that regular training has beneficial effects on insulin sensitivity and that the effect may persist for as long as 72 hours after the last bout of training (47). In addition, both aerobic training, resistance training and combined training have been shown to improve glucose control measured by HbA_{1c} (22,44,56,57). It appears that the volume of training is linked to improvements in HbA_{1c} (58). Prolonged physical activity and training elicit adaptation in insulin action leading to increased insulin sensitivity along with increased concentration of glucose transporters and improved fat consumption, which leads to enhanced blood glucose control and a better fat profile (59).

2.2 Oxidative stress and inflammation

An acute bout of training elicits an increase in both proinflammatory markers and oxidative stress, which, in turn, leads to adaptation in the defence against inflammation (19). Hence, studies have shown a reduction in inflammation markers after a prolonged period of regular physical activity (26,60,61). Interleukin-6 (IL-6) is thought to be involved in this anti-inflammatory mechanism (62). When exercising, the muscle acts as an endocrine organ, secreting IL-6 into the bloodstream. This stimulates the secretion of other anti-inflammatory cytokines and thereby inhibits pro-inflammatory cytokines such as TNF-α (62). The concentration of the hormone adiponectin is also increased owing to training. Adiponectin increases insulin sensitivity. The effect of physical activity and training is summarised in Figure 2 (26). Figure 2 shows how training exerts its function in multiple sites by delaying or preventing development of overt T2D from insulin resistance. As can be seen in the Figure, the development of T2D from insulin resistance is related to hyperglycaemia (glucotoxicity) and elevated concentrations of free fatty acids in the blood (lipotoxicity). This can lead to both oxidative stress and low-grade inflammation. Oxidative stress occurs when the reactive oxygen species exceeds the antioxidative defence, which can entail tissue damage (Betteridge, 2000) and is linked to the development of T2D (Teixeira, 2012). Training prevents development of oxidative stress (Teixeira, 2012). Low-grade inflammation is also linked to development of T2D and is caused by high levels of cytokines (Teixeira, 2012). In Figure 2, the arrows related to cytokines and adiponectin are reversed, as the effect of training causes a lower concentration of cytokines and elevation of adiponectin and not lipotoxicity. In summary, training plays an important role in preventing or delaying the development of T2D.

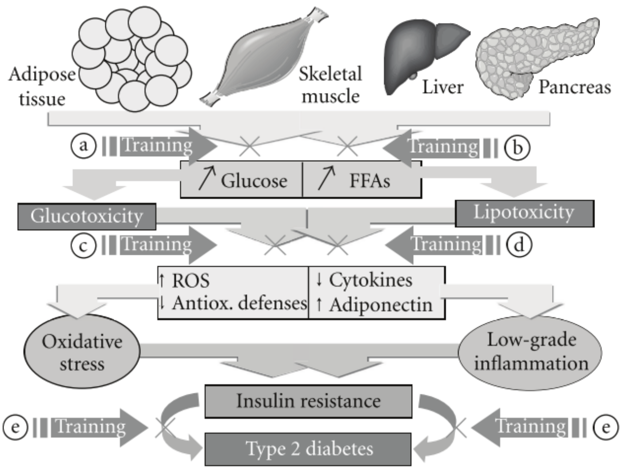


Figure 2: Summary of the effect of physical activity and training (26).

Because of these beneficial effects, the ADA recommends 30 minutes of moderate-to-vigorous-intensity aerobic training at least 5 days a week or a total of 150 minutes per week (45). This is in line with the recommendations from the Danish Health Authority (63). As for resistance training, two times per week is recommended at moderate to vigorous intensity (45).

2.3 Contraindications

Although physical activity and training are highly relevant in the treatment of T2D, some precautions are warranted regarding participation in physical activity and training. In general, if blood glucose concentration increases to 17 mmol/l, physical activity should be postponed. This also applies to blood glucose concentrations below 7 mmol/l if insulin therapy is provided to avoid hypoglycaemia. A blood pressure above 180/105 contraindicates physical activity and training as long as no pharmacological treatment is initiated. If both hypertension and proliferative retinopathy is present in patients with T2D, it is recommended to refrain from HIT and training that includes Valsalva manoeuvres. Furthermore, if patients suffer from neuropathies and have increased risk of foot ulcers, no body-bearing activities should be included in the physical activity and training. In the case of autonomic neuropathy, it is of importance to know that neuropathy can be related to silent ischaemia. In these cases, patients often suffer from orthostatism, resting tachycardia and poor thermoregulation. Consulting a cardiologist is advised before physical activity and training. (Klarlund, 2015)

2.4 High-intensity training

HIT is a relatively new training method used in the treatment of diseases like T2D. Interest in HIT is based on its timesaving potential, as following a HIT protocol is less time consuming than following a moderate-intensity protocol. This has raised the question if HIT is as efficient as the well-documented moderate-intensity training and if there is sufficient evidence for the positive effects of HIT on T2D. A meta-analysis concluded that HIT has the potential to improve cardiometabolic factors in patients with T2D and that HIT can be used as an effective supplement to a lower-intensity continuous training program (64,65). Some of the positive effects include an increase in the concentration of glucose transporters (GLUT4) (66), improved OGTT and HOMA-IR (a measure for insulin resistance) (67–70), lowered HbA_{1c} (67,69–71) and improved cardiac function in relation to endothelial-dependent vasodilator response and functional capability (72) as well as cardiac structure (73). These results are based on the effects of different HIT protocols on patients with T2D. As a result, Wormgoor et al. (2017) stated that "*HIIT is a therapy with benefits at least equivalent to moderate-intensity continuous training; hence, HIIT should be considered when prescribing training interventions for people living with type 2 diabetes*" (74). Furthermore, HIT has been shown to improve aerobic fitness and to reduce risk factors related to T2D (75), and to elicit higher enjoyment than moderate-intensity training in healthy subjects (76).

Concern has been raised about the feasibility and tolerance of HIT due to its high intensity. Some studies used training protocols with all-out sessions (The Wingate protocol) in healthy persons (77–79). However, the prevalence of high BP in patients with T2D led to the development of training protocols using a lower intensity than 100% of maximum heart rate (HR_{max}). Studies examining these protocols indicate that HIT is feasible and well-tolerated in patients with T2D (66,80,81) when no contraindications are present. Based on this knowledge, HIT appears to be both effective and feasible in the treatment of T2D, even when a less strenuous protocol than the all-out Wingate protocol is used.

Despite overwhelming proof of the positive effects of training, it remains a challenge to get patients with T2D to meet the recommendations of regular physical activity. This is supported by a study showing that 60% of patients with T2D in the U.S. did not meet current guidelines (82). These guidelines recommend:

"*150 min or more of moderate-to-vigorous intensity activity weekly, spread over at least 3 days/week, with no more than 2 consecutive days without activity. Shorter durations (minimum 75 min/week) of vigorous intensity or interval training may be sufficient for younger and more physically fit individuals"* (45)*.* Furthermore*, "adults with diabetes should engage in 2–3 sessions/week of resistance exercise on non-consecutive days*" (45).

The lack of participation in regular training and physical activity is often reasoned on lack of time (83,84); an objection which is taken into account by the HIT approach. The introduction of technology in daily life could be a means of addressing this lack-of-time challenge by enabling patients to train at time and place most suitable in their daily life.

The use of technology to further physical activity and training will be presented in section 4 in this thesis. Adding technology to HIT would not be time-consuming *per se*. Connecting technology tracking the HIT performed with a health professional allows the patient the possibility of getting supervised training and while still training whenever and wherever it suits him or her.

2. Physical activity and training

3. Setting

The beneficial effects of physical activity and training previously mentioned will emerge only if training is performed as prescribed. As large numbers of patients with T2D are inactive (82), some incentives may be necessary to encourage them to train. National clinical recommendations in Denmark related to T2D are the basis for treatment of T2D. According to these recommendations, training should be part of the treatment offer to patients with T2D (85). The clinical recommendations are incorporated into the health agreement formulated by the Danish Regions and municipalities as codified in Danish Health Legislation to ensure coordination and continuity of care for patients in Denmark (86,87). As the agreements are formulated in collaboration between the Danish Regions and the municipalities, some variation between agreements will occur, but all health agreements must be approved by the Danish Health Authority, which bodes for their general compliance with the statutory prescriptions. As the setting of this PhD project is Aalborg Municipality, the following section will focus on this municipality.

In Aalborg Municipality, patients with T2D are offered an 11-week rehabilitation course in Sundhedscenter Aalborg pending referral from a general practitioner (GP). This rehabilitation focusses on patient education, training and diet. Patient education takes the form of a rehabilitation course, which is introduced as follows (translated from https://sundhedscenter.aalborg.dk/kronisk-sygdom/diabetes-type-2):

“We offer you a free 11- week course that can help you change your habits in a healthier direction.

During the course, you will get education in different topics such as handling your medicine, physical training, diet and nutrition. Besides education, you will get a personalised training plan and we will supervise your training.

This is how you start

To attend this course, you need a referral from your general practitioner or from the treating hospital. When we receive the referral, we will invite you to an introductory meeting.

During this meeting, we will create a plan, taking your wishes and needs into consideration. The plan can include:

- *Support and guidance from a nurse, physiotherapist and dietitian*
- *Education 1 time/week*
- *Physical training 2 times/week*

- *An offer of dietary guidance and smoke cessation"*

As adherence to the treatment regimen in general and physical training in particular represents a challenge for patients with T2D as discussed above, it is important to continuously rethink how the design of the rehabilitation offer can best support overall adherence.

3.1 The rationale behind the PhD project

Expanding the current rehabilitation offer so that it encompasses a more diverse patient group and draws on a concerted, interdisciplinary effort in order to improve adherence and patients' self-management abilities could prove productive. It is therefore suggested that the present program be expanded as follows:

- The type of training offered should encompass HIT, which is more time saving yet just as efficient as traditional training.
- The venue for physical training should be flexible, allowing patients to train at home or in another self-elected venue in order to increase their freedom to decide on his or her own when and where to train.
- Monitoring should also include self-monitoring, allowing patients themselves to follow the diabetes-related improvements obtained by training.
- The rehabilitation process should be facilitated by technology to allow healthcare professionals to interact with more patients and enable patients to get supervision on their training.
- Screening should be introduced to appraise the patient's health literacy level and attitude towards diabetes with a view to identifying patients in need of tailored supervision.

We posit that adding these dimensions to the existing rehabilitation offer could likely increase treatment adherence and increase the patient's own responsibility for his or her health. A way to incorporate these additions could be by integrating technology into rehabilitation. Therefore, some focus should be attended towards the usability of technology in this matter.

Before addressing this issue of technology and in light of the present study setting, we will briefly introduce the research questions, and then in Chapter 5 continue the discussion of how technology.

3.2 Research questions

The setting and the rehabilitation program offered are critical to achieving the beneficial effects of physical activity and training. On this backdrop, the following two main research questions were raised:

- Which tendencies are detected in the association between HIT and diabetes-related outcomes measured with the use of simple self-monitoring methods (Question 1)?

- Is a home-based HIT protocol with technology-based supervision for patients with T2D feasible related to intensity and frequency of training. Furthermore, do health literacy and attitudes towards diabetes affect adherence to HIT (Question 2)?

These research questions and the studies conducted to answer the questions will be presented in detail in section 5.

3.Setting

4. Technology

4.1 Definitions of technology

Technology has undergone rapid development in recent years and has become more sophisticated and more widely accessible. In the present PhD project, the technology considered is that of eHealth and telehealth/telemedicine.

The term "eHealth" was defined by Eysenbach in 2001 and later adjusted by Pagliari et al (2005) (88,89):

"eHealth is an emerging field of medical informatics, referring to the organization and delivery of health services and information using the Internet and related technologies. In a broader sense, the term characterizes not only a technical development, but also a new way of working, an attitude, and a commitment for networked, global thinking, to improve health care locally, regionally, and worldwide by using information and communication technology."

Telehealth and telemedicine are collective names for technology and are defined by the WHO:

"…falls under the broader term of eHealth and involves the delivery of healthcare services, where distance is a critical factor. The telemedicine approach uses information and communication technologies for the exchange of information for diagnosis, treatment and prevention of diseases and injuries, research and evaluation, and for the continuing education of healthcare providers." (90,91).

The following sections will look into the use of technology for monitoring diabetes-related outcomes and increasing physical activity. Furthermore, the use of technology to increase adherence and self-efficacy will be presented. The studies referenced in the following section are based on patients with T2D unless otherwise stated.

4.2 Technology and monitoring of diabetes-related outcomes

As mentioned earlier in this thesis, it is critical to establish and maintain proper glucose control to prevent disease progression and development of complications. Furthermore, it has been found that self-management and self-care are important in the treatment and control of T2D (92). This is supported by Norris et al. (2001), stating that self-management training in patients with T2D is effective, and Heinrich et al. (2010) who reported a positive effect of self-managed training on quality of life related to diabetes (93,94). The use of technology may play a positive role concerning self-management and self-care, and research has been conducted to study if the use of technology could be beneficial in improving diabetes-related outcomes such as Hba_{1c}.

A study on web-based care management in patients with poorly treated diabetes found that web-based management was associated with a larger decrease in HbA_{1c} than standard care and education (95). Software using real-time feedback is also reported to be positively associated with a decrease in HbA_{1c} (96), and an improved effect on glycaemic control was found with the use of secure messaging between patient and care providers; moreover, this improvement was associated with an increase in the number of outpatient visits (97). Other studies have also detected improvements in HbA_{1c} with the use of SMS (98–100), SMS in an educational intervention (99) and an online self-management system (101).

To summarize, it appears that the potential of technology in diabetes care is related to its use for monitoring of diabetes-related outcomes. The next question that begs itself is therefore whether technology can be used to increase physical activity.

4.3 Technology and physical activity

Several studies have investigated the use of technology in relation to physical activity, and technology seems to have potential for improving physical activity. A review by Connelly et al. (2013) concluded that significant changes in physical activity were obtained when combining internet-based interventions with additional methods such as personal email support and logbooks (102). Also, personalised-text messages, smartphone-app and internet self-management programs have shown increased engagement in physical activity, increased physical activity and a potential to change behaviour in patients in primary care (103) and patients with T2D (104,105). Other studies used a pedometer, which led to an increased number of steps/day (106,107) and a positive change in the primary care patients' perception of physical activity (108). A review by Van den Berg et al. (2007) concluded that physical interventions using the internet were more effective than waiting lists (109). Even so, Jennings et al. (2014) found that maintaining an increase in physical activity using a web-based intervention in patients with T2D was challenging (110).

Clinicians' use of a mobile phone to provide guidance related to physical activity to participants at risk of metabolic syndrome has also been studied (111). The participants used the mobile phone to transmit data on blood pressure, blood glucose, weight and steps to the clinical team. Use of a mobile phone increased physical activity after 8 weeks of intervention (111). An increase in physical activity was also found in patients with T2D and chronic obstructive pulmonary disease (COPD) who used a tool consisting of an activity tracker, a mobile phone app and a Web app (112). This tool was combined with regular consultation with and feedback from a practice nurse (112). Feedback was also combined with an app in the initial phase of a study by Plotnikoff et al. (2017)(113). Even though the feedback ceased after the initial phase, the app alone was concluded to facilitate physical activity in patients with T2D (113,114). Also, Tate et al. (2015) conducted a review of the use of technology, self-monitoring and physical activity, concluding that interventions to enhance self-monitoring were more effective in promoting physical activity if at least one kind of technology was used as support, and that the use of interactive technology to encourage self-management and behavioural change is beneficial (115).

Taken together, these studies imply that technology shows potential for increasing physical activity in patients with T2D. Even so, it is important to keep in mind that adherence to treatment is crucial to maintaining the positive effects obtained from physical activity and training. Therefore, to counteract non-adherence to treatment, it is relevant to gain more knowledge about factors affecting adherence.

4.4 Adherence

For many patients with T2D, it remains a challenge to change lifestyle and to adhere to the treatment regime even in the face of abundant evidence of the beneficial effects of physical activity and healthy diet. Adherence to the treatment regime of T2D is crucial to preventing further progression and complications of the disease, and non-adherence influences both health outcomes and health care costs (116–119). Treatment of T2D relies mainly on the patient's self-care, so it is of importance to focus on barriers to treatment adherence. Such barriers include, among others, health literacy, beliefs and attitudes (120). These terms will be further described after presenting the definitions of adherence.

4.4.1 Definition of adherence

The definition of adherence used by the WHO is based on definitions proposed by Haynes and Rand:

"*the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider.*" (121)

It should be noted that the definition adherence captures the extent to which the patient agrees with the recommendations given (WHO: adherence to long-term therapies) instead of focusing on just following the treatment, thereby using a more patient-centred approach (121).

4.4.2 Health literacy

Health literacy refers to the ability to understand medical information and treatment, and understanding is very important to adherence (120). A definition of health literacy has been proposed by the WHO:

"The cognitive and social skills which determine the motivation and ability of individuals to gain access to, understand and use information in ways which promote and maintain good health" (122).

This definition shows that health literacy is key to benefit from health information, and that inadequate health literacy can influence both the individual and society, leading to incorrect use of medications, ill-informed healthcare decisions, etc. (123). Nutbeam (2000) divided health literacy into three levels: a functional level, an interactive level and a critical level. The functional level is described as the most fundamental level, as it refers to the ability to read, write and understand numbers (124). The relation between health literacy and adherence is discussed in a review by Martin et al. (2005), who concluded that the risk of non-adherence was high when the functional level of health literacy was low (120). Therefore, the use of health literacy in this PhD project will focus on the functional level with the use of the Danish test of Functional Health Literacy in Adults (TOFHLA) (125,126).

4.4.3 Belief

Health literacy is one of the factors modifying the patient's beliefs according to the health belief model (HBM) (120). The HBM shows the concepts involved in explaining and predicting preventing health behaviour (Figure 3).

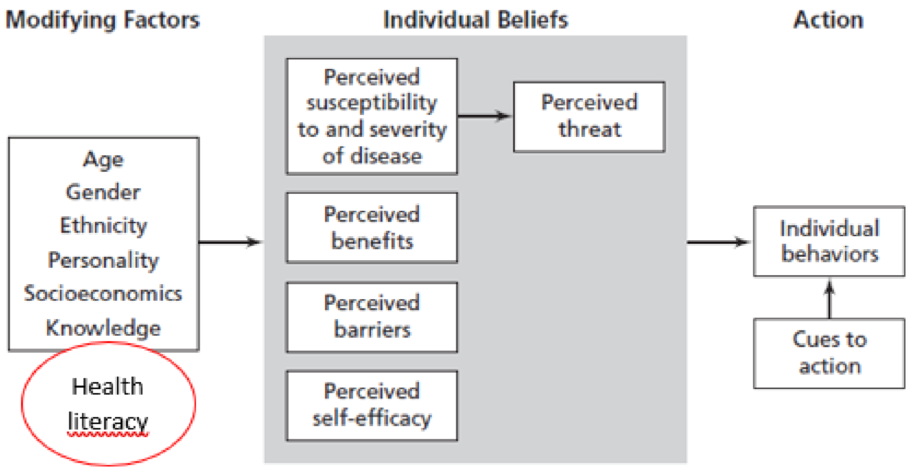


Figure 3. Modified version of the HBM (127).

Overall, the model states that a person will only try to change a health risk behaviour if the person believes that he or she is susceptible to a disease and that that disease can severely affect some component of life. The change in health risk behaviour should then be beneficial in reducing the susceptibility and severity. Furthermore, the barriers towards the behavioural change should not exceed the benefits (127,128). The model shows that individual beliefs can be affected by several modifying factors such as age, gender, ethnicity, personality, socioeconomics, knowledge and health literacy. Changing health behaviour is influenced by both the individual beliefs and by cues to action. The individual's beliefs encompass several factors as described by Rosenstock in 1974 (128):

- The perceived risk of getting the disease (susceptibility) and the seriousness of the disease (severity) which affect the perceived threat.
- Perceived benefits refer to the usefulness of a new behaviour in decreasing the perceived threat
- Perceived barriers refer to the negative aspects of a behaviour (e.g. time-consuming, inconvenience and unpleasant)
- Perceived self-efficacy refers to "*the conviction that one can successfully execute the behaviour required to produce the outcomes*" (127).

The likelihood of changing behaviour to avoid the perceived threat is affected by the perceived benefits, perceived barriers and level of self-efficacy (127,128). To enhance T2D patients' adherence to physical activity and training, it is therefore important to identify and diminish any such perceived barriers. In addition, attention should be payed to enhancing self-efficacy, as it is an important factor related to adherence as well.

4.4.4 Attitude

Attitude is also a potent co-player in adherence to a treatment regime. A link between the attitude towards diabetes and adherence to treatment has been described by Anderson et al. (1993) (129). They developed and revised the Diabetes Attitude Scale (DAS) as a tool for establishing the attitude of both patients with diabetes and health-care providers (130) based on a connection between a positive attitude and a higher level of adherence (129). DAS is based on the theory of reasoned action and the theory of planned behaviour, which state that the *intention* to adhere is essential to following a treatment regime (131,132). These theories can be used to predict a person's intention to engage in a certain behaviour. Attitude here refers to the person's attitude towards the behaviour and the outcome of the behaviour (131). Each individual harbours a subjective norm, which refers to the approval or disapproval of the behaviour from people of importance such as family, friends and healthcare providers (131). Perceived behavioural control is the shift from the theory of reasoned action to the theory of planned behaviour and refers to the perception of how easy or difficult it would be to perform the behaviour (131,132). The influence of attitude on behaviour is depicted in Figure 4.

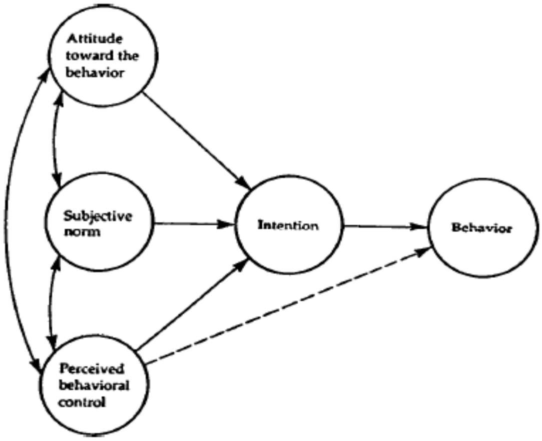


Figure 4: The influence of attitude on behaviour (131). (Theory of planned behaviour (131)).

Thus, it is of interest to acknowledge attitude as an important co-player in adhering to a behaviour and treatment.

To summarize, adherence to a treatment regime is connected to health literacy, beliefs and attitudes. In the attempt to increase adherence, these factors are of relevance, and the question is if technology could be a method of increasing factors positively related to adherence.

4.5 Technology in relation to adherence

The present section will describe studies of how technology could be beneficial in increasing patients' adherence to physical activity.

Improvements related to self-efficacy were observed in interventions using mobile phones in health care (133), and it is of interest as low self-efficacy and self-care behaviours have been reported in patients with T2D with poor glycaemic control (134). In the review by Krishna et al. (2009), the role of mobile phones in diabetes care was studied with a particular focus on the use of mobile phones' voice and text messages (133). Different types of diseases were included in the review; in relation to diabetes, an association between the use of text messages via a mobile phone and improved self-efficacy and adherence in young people with type 1 diabetes (T1D) was reported, even though no improvements in glycaemic control were detected (135). It is noteworthy that the result is based on young people with T1D, and no direct connection can be made to patients with T2D. However, the result demonstrates that improved self-efficacy and adherence are obtainable with the use of text messages; and this effect has the potential to be transferred to other groups of patients such as patients with T2D. This potential is supported by a study showing that factors related to self-efficacy, social support and health belief improved with the use of a mobile phone-based intervention in patients with diabetes (both type 1 and 2) (136). A positive effect on self-efficacy was also found using text messages to enhance self-care behaviours in patients with T2D (137).

The use of technology to increase adherence to physical activity and training has also been studied.

Using a pedometer to set goals for physical activity and to provide feedback after training sessions showed a high level of adherence (89 +/- 4%) despite a high training load (4 times/week, 60 min/session) for a relatively long training period (4 months) in a free-living setting (138). A simple app for smartphones increased physical activity in patients in primary centres (103); and a review by Sallis et al. (2015) concluded that compliance with physical activity recommendations can be improved with the use of technology like accelerometers and smartphone applications (139).

The most important factor in a prevention program appears to be sustainability (55). It is therefore possible that technology could be instrumental in increasing such sustainability. Support for this argument may be found in a review by Sallis et al. (2015), which concluded that compliance improved by using evolving technology like accelerometers and smartphones applications (139). Furthermore, in older patients with diabetes, a lesser decline in physical activity levels was shown when technology was used than in patients not using technology (140). Using community features where participants can communicate with each other was not associated an increase in number of steps, but withdrawal from the study decreased (141).

In conclusion, it appears that technology is a potent tool in the treatment of T2D; both in relation to measuring, increasing and adhering to physical activity. However, it is important that the right technology be chosen, i.e. technology that is useful in a clinical setting and not only in a research setting. This means that the answers obtained by use of the technology should provide useful and relevant clinical information and at the same time be easy to use, access and read (142). Using technology could be a way of enhancing training flexibility in terms of when and where to train; and, as mentioned earlier in this thesis, HIT could be timesaving as well as efficient as a training method. Combining technology and HIT now gives us the opportunity to spend less time on exercising and to train when and where it suits the patient and still monitor the training. The following section will describe how this combination has been the focus in the studies in this PhD project.

4.Technology

5. Aims and overview

This section will describe the overall objective and research questions of the PhD project. Furthermore, the aims of the studies conducted to answer the research questions will be presented.

5.1 Overall objective

The overall objective of this PhD project is to develop a new approach to diabetes management encompassing technology-based, supervised home-training using a timesaving HIT protocol and simple self-monitoring methods to measure improvements in diabetes-related outcomes. A further aim is to study if health literacy and attitudes towards diabetes have an impact on adherence to training at home. Specifically, the two main research questions were:

- Which tendencies are detected in the association between HIT and diabetes-related outcomes measured with the use of simple self-monitoring methods (Question 1)?

- Is a home-based HIT protocol with technology-based supervision for patients with T2D feasible related to intensity and frequency of training, and do health literacy and attitudes towards diabetes affect adherence to HIT (Question 2)?

To answer these questions, four studies were conducted. Study 1 and 2 were conducted to answer Question 1. To answer Question 2, the training protocol from study 1 and 2 were used in Study 4 as well as the translated DAS from the task-driven Study 3. Figure 1 depicts the overall aims of the four studies and the research questions related to the study. A more detailed summary will be presented in the next section.

5. Aims and overview

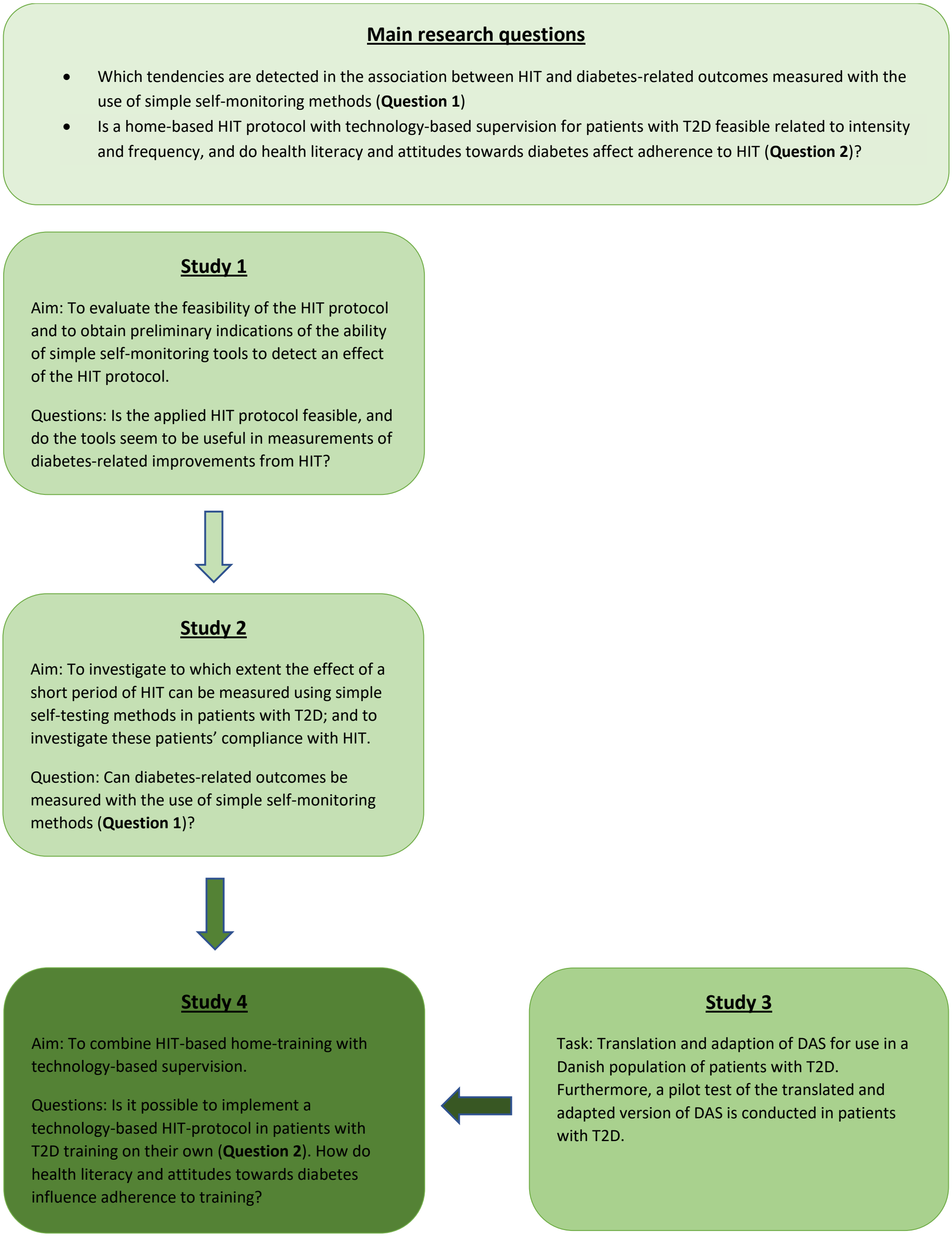


Figure 5: Overview of the studies in this PhD project.

This figure shows how the studies in the present problem-based PhD project are connected. First, a pilot study aimed at testing the study protocol in relation to the feasibility of the training protocol and to evaluate the use of simple self-monitoring methods was conducted. The pilot study led to minor changes in the study protocol, which was applied in Study 2. The next step was to investigate if patients with T2D could perform HIT at home with supervision using technology. Furthermore, we looked into a possible connection between health literacy, attitudes towards diabetes and adherence. To include attitudes towards diabetes, it was necessary to perform problem-driven research (Study 3) and to translate and adapt a questionnaire to a Danish setting before applying it in Study 4. Study 1 and 3 are pilot studies that aimed to test the study protocol and to get preliminary results. Therefore, the sample size of these studies is small.

This PhD project was carried out as problem-based research. The concept of problem-based research implies that a societal issue is defined outside the scientific community (143); this approach to research is often both problem oriented and problem driven. Thus, the concept ”problem-based” is used here an overarching term. The problem in this PhD project is that despite solid evidence for the positive effect of physical activity and training on T2D, a large number of patients with T2D remain inactive. This led to the overall aim of the PhD project which is to study how elements may be added the existing rehabilitation offer to improve adherence.

A more traditional hypothesis-driven research could also have been deployed. In hypothesis-driven research, hypotheses are defined with the aim of testing a specific explanation (144). These hypotheses are an assertion of a causal relationship (145). Studies are then made to collect data to confirm or reject the hypothesis. In the case of a more traditional hypothesis-driven research, possible hypotheses could have been raised in relation to quantitative or qualitative effects of training or the willingness and capability of patients to engage in this type of training. These hypotheses are seen in Table 2.

Table 2: Presentation of the hypotheses of the PhD project.

	Hypothesis
Overall, the entire PhD project	Changes in diabetes-related outcomes after a period of HIT can be measured with simple self-monitoring methods.

5. Aims and overview

Overall, the entire PhD project	Technology can be used to provide supervision for patients with T2D performing HIT at home. Health literacy and attitude towards diabetes affect adherence to HIT
Study 1: The use of self-monitoring methods in a high-intensity training study on patients with type 2 diabetes: A pilot study.	1. Simple self-monitoring methods show may be used to detect effects of a short training period using a HIT protocol. 2. The HIT protocol is feasible in patients with T2D.
Study 2: A self-monitoring approach for evaluating the effect of 3 weeks of high-intensity training in patients with type 2 diabetes mellitus. An intervention study.	An effect of HIT can be detected using simple self-monitoring methods after a short training period.
Study 3: Translation and adaption of the Diabetes Attitude Scale (DAS) for use in patients with type 2 diabetes in Denmark. A pilot study.	DAS can be translated and adapted to a Danish population of patients with T2D.
Study 4: Evaluating a HIT-based home-training program with technology-based supervision. A mixed-method study.	1. Patients with T2D can reach the right training intensity in terms of both training intensity and training frequency when training a home for 5 weeks. 2.a The technology used to supervise training is well evaluated.

	2.b Health literacy and attitude towards diabetes influence adherence to training in terms of intensity and frequency.

5. Aims and overview

6. Summary of studies

This section will give an account of the rationale behind the studies in relation to study design and methods. Furthermore, a summary of the aim, methods, results and discussion/conclusion of each study will be presented. Further details can be found in the individual papers.

6.1 Rationale behind the studies

This PhD project includes two pilot studies. Pilot studies are defined as smaller versions of a main study, and they are conducted to allow the researchers to gain knowledge about the methods and any requisite changes in methods before applying them on a larger scale (Eldridge, 2016). Furthermore, preliminary results can be obtained, and the analysis process can be prepared and tried out (Eldridge 2016, Doody, 2015). Reporting these finding allows other researchers to learn any lessons made in the pilot study, wherefore conducting and reporting pilot studies is an important part of healthcare research (Doody). A distinction is often made between a pilot study and a feasibility study, where the latter seeks to answers the question whether a future study can be done, if it should be done and how it should be done (Eldridge et al, 2016). A pilot study, on the other hand, is more focused on design (Eldridge, 2016). Even though these definitions apply to randomised control studies (RCT), they may certainly also be used in the context of non-randomised feasibility and pilot studies (Eldridge 2016).

In relation to the present PhD project, Study 1 was a pilot study aiming at trying out the test protocol before applying it on a larger scale to evaluate if changes in the methods needed to be made. Furthermore, the study gave the researcher the opportunity to try out the method and to become experienced with the method. In Study 1, the result obtained gave rise to changes in the protocol related to the day of week at which the tests were performed before using the method in Study 2. Also, Study 3 was also a pilot test in which the researchers aimed at learning the method used to validate the DAS-3. The experiences from this study are reported and should be included in future studies at larger scales. In Study 4, a technology was used to track the training and as a tool to give supervision. This particular part of the study could be defined as a feasibility study as it focused on the expediency of using a technology in the setting given of Study 4, and the results from the study should be used to find or develop the most suitable technology for this purpose.

The technology deployed in Study 4 was used to record the training and to give supervision. Usability is defined as *“The extent to which a product can be* *used by specific users to achieve specified goals with effectiveness, efficiency and satisfaction in a specified context of use"* (146). Usability is an important element is any successful implementation and as stated by Nielsen (1994), good usability refers to a system that "*is easy to learn, efficient to use, easy to remember, generates very few errors, and leads to great user satisfaction*" (147). The technology used in this PhD project was not tested for usability. This could influence the participants' use of the technology. If usability was poor, this could affect the participants' ability to use the technology properly and thereby affect the results of the study. This was sought avoided by a thorough introduction to the technology and by giving participants the possibility to contact the principal investigator if problems occurred. Also, the principal investigator contacted the participants if any data were lacking to clarify if this was due to problems with technology. Future studies should include tests to ensure good usability.

The rehabilitation offer in Aalborg Municipality has a duration of 11 weeks. In Study 4, a shorter duration was chosen (5 week) partly for practical reasons and partly to study adherence in the first weeks where participants' motivation is expected to be highest. Furthermore, one of the aims of the study was to evaluate if the participants were able to keep the right frequency of training for a longer period and not to copy the duration of the rehabilitation offer.

6.2 Inclusion and exclusion criteria

The inclusion and exclusion criteria were the same in Study 1 and 2, and to be included manifest T2D had to be diagnosed. In addition, specifically for Study 2, it was required that the participants were able to attend the fixed test days as well as training days. In relation to exclusion criteria, patients with a pacemaker were excluded due to the risk of interference with the equipment used. Furthermore, patients were excluded if conditions contraindicating HIT were present. To ensure that no such conditions were present, the participants were asked to consult their GP before the onset of the study to acquire the GP's oral approval.

Study 3 included patients with T2D with the ability to read and understand Danish.

To be included in Study 4, a diagnosis of manifest T2D made by the patients' own GP had to be present. Moreover, the possession of a mobile phone was required. This phone needed to be compatible with the used equipment. Any conditions contraindicating HIT were set as exclusion criteria. The participants were asked to consult their GP before inclusion to avoid the presence of such conditions.

6.3 Summary of study 1

The use of self-monitoring methods in a high-intensity training study on patients with type 2 diabetes: A pilot study.

Aim: The aim of this pilot study was to evaluate if a HIT protocol was feasible in the eyes of patients with T2D. Furthermore, the pilot aimed to obtain preliminary results of using simple self-monitoring methods to measure diabetes-related changes after a period of HIT.

Methods: The study included six patients with T2D. Before and after a training period, the participants completed a test battery including simple methods easy to apply by the patients themselves in a daily setting. The selected methods included maximum rate of oxygen consumption (VO_2max), OGTT, blood pressure, fat percentage, weight and a questionnaire related to physical activity. The training period consisted of six HIT sessions, each consisting of 10 intervals of 1 minute at 90% of HR_{max} interspersed with 1 minute of low-intensity (~50 watts) training on an ergometer bike.

Results: All participants completed the training period and reached an acceptable level of intensity during training. Interpretation of the results related to glucose control was challenging as the changes were not uniform. Both diastolic and systolic blood pressure decreased, and only a few changes in fat percentage and weight were observed. VO_2max rose for all six participants. The test day was not standardised.

Discussion/conclusion: All the participants in this small-scale pilot study seemed to tolerate the applied HIT protocol as no side effects were reported. The diversity of the results related to glucose control led to speculations on the possibility that the day of the test could influence the results. Therefore, the pilot study led to changes in the protocol so that a standardised test day was used in the protocol in the next study. The pilot study showed the potential of measuring beneficial HIT-induced training effects in patients with T2D with the use of simple self-monitoring methods.

6.4 Summary of study 2

A self-monitoring approach for evaluating the effect of 3 weeks of high-intensity interval training in type 2 diabetics. An intervention study.

Aim: The aim of this study was to study if the effect of a short period of HIT could be measured by using simple methods that the patients with T2D easily could learn to use and interpret by themselves. Furthermore, the study aimed at investigating these patients’ compliance with HIT.

Methods: The second study used the revised protocol from the pilot study and included ten patients with T2D. The test-battery included OGTT, VO_2max, blood pressure, fat percentage and weight. In addition, the participants completed two questionnaires related to physical activity and co-morbidities. The training period consisted of eight HIT sessions. Each training session included ten 1-minute intervals of 90% of HR_{max} interspersed with 1 minute of low-intensity training. A warm-up period of 3 minutes and a cool down period of 2 minutes were also included in the training protocol. Table 3 shows an overview of the pre-test, training period and the post-test.

Day	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Activity	VO_{2max}		Base line			T		T		T			T		T		T			T		T		Post-test

Table 3: Overview of pre-test, training period and post-test. T: training

Results: All ten patients completed training at an acceptable intensity, and no adverse effects were recorded. A significant decrease in 2h glucose concentration as well as diastolic blood pressure and weight were measured. No significant changes in fasting glucose, systolic blood pressure and fat percentage were observed.

Discussion/conclusion: The study showed improvement in the effects of HIT on T2D-related outcomes in T2D patients with the use of simple self-testing methods. These results open the perspective of enabling patients with T2D to measure progress on their own and thereby support patient motivation and further self-efficacy.

6.4.1 Study 2 – revisited

Study 2 was published before the present PhD thesis was submitted. The preparation of submission of the thesis and the appertaining studies have given us a number of novel insights that are communicated below.

In accordance with the aim of the study, we formulated the following research question: Can an effect in diabetes-related outcomes from HIT be detected using simple self-monitoring methods?

Given the fact that glycaemic control is pivotal for patients with T2D and that glycaemic control can be improved by performing HIT, the primary outcome of this study is considered to be both glycaemic control (in this study measured by fasting glucose and 2-h glucose concentration) and training intensity.

Method: All participants were recruited from the Sundhedscenter Aalborg, where the physiotherapist contacted relevant participants. The next step was to establish contact between the participants and the principal investigator to obtain detailed information. No data are available describing this process. In retrospect, inclusion of such data could have given valuable information related to reasons why subjects may not have been included in the study.

Data are presented as mean and range for the baseline values. The mean difference between baseline and post-test is presented with 95% CIs.

The parametric paired t-test was used to calculate the significance between baseline and post-test measures. Statistical significance was considered if p-values < 0.05.

Results:

Table 4: Physical values at baseline; the mean difference and the corresponding p-value using a paired t-test (A corrected version of Table 2 in the submitted paper).

	Baseline		Mean difference	p-value
Weight	Mean	108.3±14.7	-0.8 CI: -1.6 - 0.0	0.05
	Range	85.6-128.3		
Total fat	Mean	31.8±5.8	-0.3 CI: -0.8-0.3	0.31
	Range	24.2-39.7		
Fasting BG	Mean	7.3±2.0	-0.4 CI: -0.9-0.2	0.20
	Range	5.5-12.3		
2h BG	Mean	10.9±3.5	-1.02 CI: -1.8-(-0.2)	0.02
	Range	6-16.7		
VO2max (l/min)	Mean	2.8±0.7	4.8 CI: -172.1-181.7	0.95
	Range	1.8-4.1		
VO2max (ml/kg/min)	Mean	25.4±4.3	0.1 CI: -1.5-1.7	0.92
	Range	21.4-35.2		
Systolic BP	Mean	145.1±16.1	-8.9 CI: -19-1.2	0.08
	Range	130-178		
Diastolic BP	Mean	90.4±11.0	-5 CI: -9.3-(-0.7)	0.03
	Range	74-110		

Baseline data are presented as mean ± standard deviation (SD) and range. Mean difference is presented with 95% CI.

Use of the parametric test showed significant differences between baseline and post-test in 2-hour capillary blood glucose ($p = 0.02$) and diastolic blood pressure ($p=0.03$).

Corrected versions of Figures 2 and 3 in the published paper.

In the published version of this study, solid bars were used to show the mean of the absolute values for the participants. To show the individual changes, a new version of Figure 2 has been included. This new figure shows the changes in a more informative way.

Figure 6: Changes in glycaemic control for each participant measured as fasting blood glucose concentration and 2h blood glucose concentration (A corrected version of Figure 2 in the published paper).

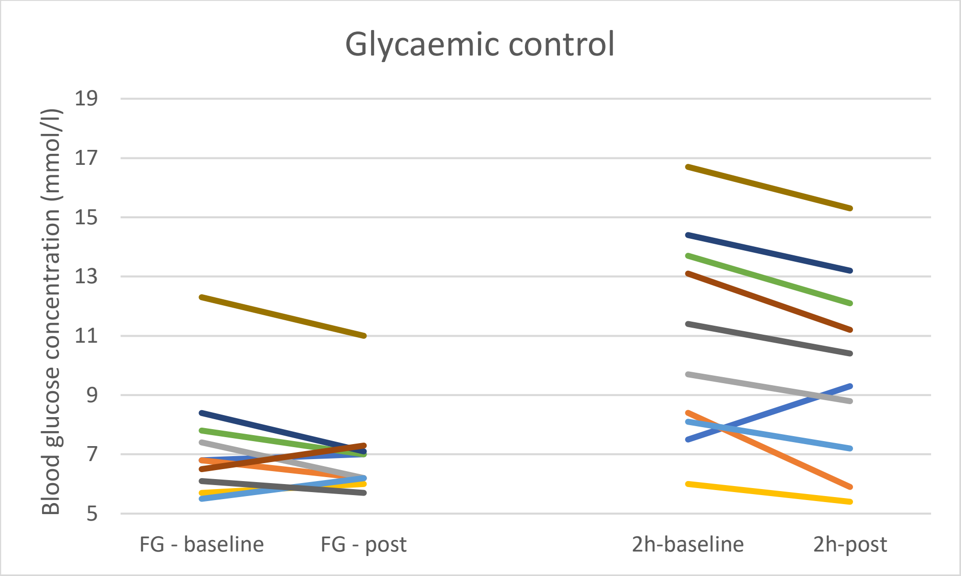
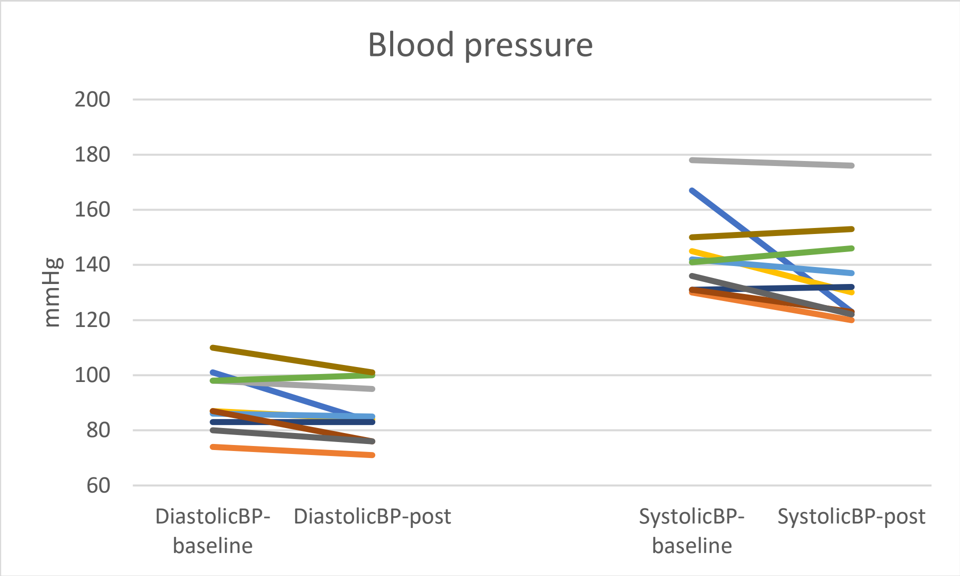


Figure 7: Changes in diastolic and systolic blood pressure for each participant (A corrected version of Figure 3 in the published paper).



Discussion: The use of differences instead of mean values in the discussion is more informative and more clearly shows the change obtained within each parameter and should have been taken into considerations.

In the published version of the paper, a non-parametric test was used (Wilcoxon signed rank test). The paired t-test uses the differences; and in a paired sample, any difference observed will normally be distributed, and a parametric test may therefore be used even when the sample size is small.

Using a non-parametric test (Wilcoxon signed-rank test) in the published paper resulted in significant differences in weight, 2h blood glucose concentration and diastolic blood pressure. In this revisited section, a parametric test (paired t-test) was used. Use of this test also showed significant differences in 2h blood glucose concentration and diastolic blood pressure. Shifting to the paired t-test showed no statistically significant difference in weight as opposed to Wilcoxon signed-rank test.

6.5 Summary of Study 3

Translation and adaption of the Diabetes Attitude Scale (DAS) for use in patients with type 2 diabetes in Denmark. A pilot study.

Aim: This study aimed to translate and adapt the DAS for use in patients with T2D in a Danish population. This process included a pilot test of the translated and adapted version of DAS with a view to including the DAS-3 in the fourth study to measure attitudes towards diabetes; hence, studies of patients participating in earlier studies detected a correlation between a positive attitude and adherence to treatment. The DAS-3 was not available in Danish and, therefore, a translation study was necessary.

Method: A translation process using the six stages in the process of cross-cultural adaption described by Beaton et al. (2000) was performed. A pilot test was conducted including 23 participants with T2D. This pilot test included a face-to-face interview aimed at establishing basic demographics. The participants then completed the test, and the attitude for each subscale was determined. The demographics were investigated, and the internal consistency and reliability of the Danish DAS were determined using statistical analysis.

Results: The participants in the pilot sample had a mean age of 56.75 years (range 36-77 years), and their diabetes age was 4.6±5.49 years. As for the internal consistency, Cronbach's alpha coefficient showed internal consistency for two of five subscales and borderline internal consistency for one subscale.

Discussion/conclusion: Based on this study, preliminary results were presented related to translation and adoption of DAS in a Danish setting, where no instruments for assessing attitude have been available. This instrument needs further validation related to both sample size and sample composition (type of diabetes, gender and age) as well as validation in health-care professionals.

6.6 Summary of Study 4

Evaluating a HIT-based home-training program with technology-based supervision. A mixed-method study.

Aim: The focus of the fourth study was to evaluate the combination of HIT-based home-training combined with technology-based supervision in patients with T2D. Several research questions were sought answered: Are frequency and intensity adequate when patients with T2D trained by themselves? How was the use of technology for supervision of the training evaluated? Did attitude towards diabetes and health literacy correlate with adherence?

Method: Before the training period, attitudes towards diabetes were measured using the DAS. Furthermore, the participants' health literacy and $VO2_{max}$ were measured. The patients then completed 5 weeks of HIT at home (3 times/week). The training protocol was similar to the protocol used in Studies 1 and 2, and the participants were equipped with a profile on Endomondo, a Polar heart rate (HR) sensor connected to their own smartphone. Each training was logged in Endomondo.

Supervision was given with the use of technology based on the frequency and intensity of training, and the feedback given was attempted standardised according to language.

The participants were interviewed at the end of the training period using a semi-structured method and asked to evaluate both the HIT and the use of technology. The themes in the interview were training, the equipment used, feedback in relation to the use of the app and miscellaneous.

Results: Eighteen participants (12 men and 6 women) with a mean age of 57.17±9.37 years and a diabetes age of 5.06±5.60 years completed the 5 weeks of training. The median overall attitude towards diabetes was 4 (4;4), and the health literacy was 91.59. Adherence to the training was 93.3%. The median of the training intensity ranged from 87.43% to 92.63% calculated for each participant in all training sessions. When expressed as median intensity for all intervals for each participant, the intensity was 81.52% to 97.20%.

Discussion/conclusion: The results indicate that patients with T2D can reach the right intensity and frequency of training using a HIT protocol at home. The participants in this study had an overall positive attitude towards diabetes measured by DAS, and this could explain their high adherence to training. High adherence was also related to a high level of health literacy. Despite the high adherence overall, some participants skipped training due to family issues and lack of motivation for indoor training. Other training sessions were not registered in Endomondo due to technical issues. Hence, the actual number of accomplished sessions was actually higher than appeared on Endomondo. The participants were instructed to complete 10 intervals in each session. This number varied, as some of the participants needed to adapt to training by slowly progressing the number of intervals. Still, the guidelines on both on both intensity and frequency were overall followed.

6. Summary of studies

7 Key results

The key results from this PhD study are listed below:

Study 1: *The use of self-monitoring methods in a high-intensity training study on patients with type 2 diabetes: A pilot study*

The results from this pilot study showed that the included participants were able to train at the high intensity described in the HIT protocol. Furthermore, the use of simple self-monitoring methods showed indications that they were able to detect changes in diabetes-related outcomes after a period of HIT. The pilot study led to changes in the protocol in relation to the weekday at which the test was performed.

Study 2: *A self-monitoring approach for evaluating the effect of 3 weeks of high-intensity interval training in type 2 diabetics. An intervention study*

In this study, the changes in the protocol based on Study 1 were implemented so that all participants were measured at the same day of the week. Eight times of HIT showed a significant decrease in 2h blood glucose (effect size: -1.02, p= 0.02) and diastolic blood pressure (effect size: -5, p=0.027). A decrease in weight (effect size: -0.78) was borderline significant (p=0.51). This was measured with the used of simple self-monitoring methods.

Study 3: *Translation and adaption of the Diabetes Attitude Scale (DAS) for use in patients with type 2 diabetes in Denmark. A pilot study.*

The focus in Study 3 was to translate and initiate the adaptation process of DAS to a Danish setting. The results from this pilot study in patients with T2D showed internal consistency in two of five subscales in DAS based on Cronbach's alpha coefficient (psychosocial impact of DM (Cronbach's alpha coefficient = 0.47) and patient autonomy (Cronbach's alpha coefficient = 0.33)). One subscale showed borderline internal consistency (need for special training (Cronbach's alpha coefficient = 0.7)).

Study 4: *Evaluating a HIT-based home-training program with technology-based supervision. A mixed-method study.*

The results from this study showed that the participants overall were able to perform HIT at home. This was concluded based on the intensity of training and the frequency of training among the participants. The training was supervised using technology and this was well evaluated by the participants. The attitude towards diabetes was overall positive and all but one had adequate health literacy. An association between attitude and intensity of training and frequency of training was not found. Nor was an association between health literacy and intensity of training and frequency of training established. The participants were satisfied with the use of technology.

8. Discussion

8.1 Interpretation of the main results

The interpretation of the main results will take origin in the research questions mentioned earlier in the thesis.

*8.1.2 Which tendencies are detected in the association between HIT and diabetes-related outcomes measured with the use of simple self-monitoring methods? (**Question 1**)*

Two studies were conducted to give preliminary indications on whether simple methods can be used to measure diabetes-related outcomes after a period of HIT. Other studies have established the positive effect of HIT (66,67,71,73). However, to our knowledge, no other studies have focused on the use of simple methods. Based on the results from these studies with only 6 and 8 times of training, respectively, it is suggested that it is possible to obtain positive results from HIT with the use of simple methods. Not all the used methods showed the expected improvement, which may be due to the short duration of the training period. Although we deliberately chose simple methods suitable for self-monitoring by the patients themselves, actual monitoring in these studies was performed by the principal investigator. This was done to ensure standardised measures between the participants, as the aim of the studies was to establish if a change could be detected with these methods. Future research is recommended to evaluate the level of difficulty of using the methods when used by the patients themselves. The present results only imply that measuring diabetes-related outcomes of HIT is possible, also with simple methods.

*8.1.3 Is a home-based HIT protocol with technology-based supervision for patients with T2D feasible related to intensity and frequency, and do health literacy and attitudes towards diabetes affect adherence to HIT? (**Question 2**)*

The 18 participants who performed HIT for 5 weeks at home using technology as a tool for supervision from the health professional were overall capable of obtaining a high intensity and the right frequency of training. The use of technology to monitor training and as a tool for feedback was well accepted by the participants. They all had a positive attitude towards diabetes and adequate health literacy, indicating a strong basis for adherence (123,129).

This result indicates that technology may, indeed, be used as a tool to monitor physical training and to give supervision to patients with T2D training at home.

The results of the four studies performed in this PhD project also suggest that there is potential for including both simple self-monitoring methods and technology as additions to the existing rehabilitation offer.

8.2 Methodological considerations

In this section, the considerations behind design, patient recruitment, selection of simple methods and reflections behind the use of interview and analysis of interview will be discussed.

8.2.1 Trial design

Three types of study design were used in this PhD project; intervention study, translation and adaption study and a mixed-method study.

Studies 1 and 2 were performed as intervention studies with no control group. We could have used a randomised control group, and it could be argued that a randomised controlled study (RCT) would have been a better design as it is positioned higher in the evidence hierarchy (148) because it allows safer causation assessment of the effect of intervention (149,150). An RCT compares standard treatment (or no treatment) with the new treatment and allows the researcher to discover differences in treatments (149,150). In this PhD project, the control group could either have received standard training or no training. However, a control group was not included as this PhD project focused on evaluating the use of simple self-monitoring methods and not the training *per se* (Study 2) and determining whether patients with T2D could obtain the right intensity and frequency at home with the use of technology based supervision (Study 4).

Furthermore, previous studies have established the positive effects of training in general, including the positive effects of HIT.

Study 3 was a problem-driven study aiming at translating and adapting the DAS from American into Danish. DAS determines attitudes towards diabetes and thereby predicts adherence to the treatment regime as an association between attitude and adherence has been demonstrated (Anderson 1993). Other questionnaires could have been used, e.g. the Diabetes Self-management Questionnaire (DSQM), Problem Areas in Diabetes (PAID), questionnaires related to the quality of life (SF-12, SF-36 and WHO-5), the Diabetes Intention, Attitude and Behaviour Questionnaire (DIAB-Q) and Adherence in Diabetes Questionnaire (ADQ). The DAS, the DIAB-Q and the

ADQ intend to predict engagement in self-care behaviours. In the DIAB-Q, participants are asked specific questions related to training, diet and weight loss (151); the ADQ is targeted at children and adolescents with T1D (152), whereas the DAS is more oriented towards eliciting attitudes towards diabetes (153). The PAID questionnaire focuses on the emotional factors of living with diabetes, which was not included in this PhD project's aims (154,155). As for the SF-12, the SF-36 and the WHO-5, these questionnaires are used to establish health status and psychological well-being in general and are not specifically aimed at patients with diabetes (156,157).

DAS was translated using the method described by Beaton et al. (2000) (158). As the study included patients with T2D only and the expert committee did not fulfil all the criteria proposed by Beaton et al. (2000) (158), the study is characterised as a pilot study. Furthermore, as DAS targets both T1D and T2D patients as well as health professionals, validation of the DAS was not completed. However, it was justified to used DAS in Study 4 as this study only enrolled patients with T2D. Further validation is needed before applying the DAS in patients with T1D and health professionals.

Study 4 was a mixed method study using both quantitative and qualitative data. Using a mixed method approach gives the possibility of viewing the topic of the study from different perspectives to achieve complementarity (159). No control group was included as the study focused on evaluating the combination of HIT-based home-training with the use of technology-based supervision.

In Study 4, we collected quantitative data on patients' characteristics and the intensity and frequency of training as well as on their health literacy and attitudes towards diabetes using DAS. In addition, qualitative data were obtained through semi-structured interviews at the end of the training period to evaluate the patients' experience.

Before conducting Study 4, we made a small-scale pilot study including 2 patients with T2D who also participated in Study 2. The pilot study was performed to test the technology set-up and to identify any challenges before applying the technology on a larger scale. Challenges were detected mainly in relation to the set-up of Endomondo on mobile devices, insufficiencies in the user manual and problems in connecting the HR sensor to the mobile device. The pilot study made it possible to optimize the workflow and to revise the user manual before implementation of Study 4.

8.2.2 Patient recruitment

The patients included in studies were recruited through a notice on Facebook, through Sundhedscenter Aalborg and through an advertisement in local papers. In the co-operation agreement between Sundhedscenter Aalborg and Aalborg University, it was made clear that a physiotherapist from the Sundhedscenter would perform the initial screening of the patients with T2D to identify patients who would fit the study target group. The patients included in these studies were therefore preselected, and the sample group may not reflect the variety of T2D in the population. It would have been preferable to extend the offer of participation to all patients with T2D, and therefore an advertisement in local papers was used in Study 4. That said, the average anthropometrics of the patients recruited through Sundhedscenter Aalborg reflect the general T2D patient in relation to being overweight, hypertensive and having an elevated blood glucose level as well as a low activity level. A positive effect of the preselection was the pre-exclusion related to contraindications to training as the Sundhedscenter deselected those patients whom they deemed unable to complete the training. This could have influenced the high adherence rate.

The inclusion and exclusion criteria were similar in all 4 studies with additions made for Study 3. The criteria were established to ensure that the participants enrolled in the studies were adults with T2D not suffering from conditions contradicting training at high intensities. In addition, the ability to read and understand Danish was included as an inclusion criterion in Study 3.

No dropouts were recorded in Study 1 and 2. In relation to dropouts in Study 4, 21 participants with T2D were included of whom one dropped out after the pre-test due to a novel cancer diagnosis and another participant dropped out after only one training session due to lack of motivation. A third participant completed the training period, but data for this patient were influenced by a pacemaker and could not be interpreted. The presence of a pacemaker was not known at the onset of the study. Of the remaining 18 participant, two participants ceased training before 5 weeks. One wished to run outside in the good weather, and one stopped before 5 weeks due to personal reasons. The training period was shorter in Study 1 and 2 and this could partly explain the increase in dropouts in Study 4. Furthermore, in Study 1 and 2, the training was followed more closely, as the principal investigator was present during the training. This could also have had an effect on the difference in dropouts.

8.2.3 Selection of simple methods

As the aim of Study 1 and 2 included using simple measuring methods, thorough considerations of the measuring methods were made in the inclusion process. Two criteria were set up: 1) the methods should be simple to perform, and 2) it should be easy to interpret the results. In practice, this means that patients should be able to use the methods at home, and that they should be able to understand the results obtained from the methods. We therefore chose the following methods: weight, height, fat percentage, blood pressure, fasting glucose 2h-glucose and a VO_{2max} test. The following sections will discuss the rationale behind these choices.

<u>Weight, height and fat percentage</u>

Weight and height can be used to calculate BMI (kg/cm2). This is a simple calculation, and the result can be classified into underweight, normal, overweight, and obese class I, II and III (http://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi). However, BMI is a weak and indirect measure of body composition (160). Hence, well-trained persons may be classified as obese if they have a large muscle mass, and untrained persons may be classified as normal even though they have a relatively high fat mass (160,161). We therefore combined BMI and fat percentage in the present study. Fat percentage was measured with the Tanita scale (Tanita MC-180MA, Tokyo, Japan) using bioelectrical impedance. Bioelectrical impedance uses low voltage, which is being conducted through the body. A formula calculates muscle mass, fluid status and fat mass (162). Although bioelectrical impedance is easy to use, its practical use involves several challenges. Firstly, as the human body contains 50-60% water (163); and as water is a potent conductor of voltage, the result is highly reliant on the person’s hydration status (162,164). A change in hydration status could influence the result by showing a lower fat percentage, that is a percentage that is, in fact, not due to actual loss of fat mass. Other methods could be used to measure fat percentage, including dual energy x-ray absorptiometry (DXA) scanners and fat callipers. The DXA scanner, often referred to as the golden standard for measuring body composition, is mainly used due to its ability to measure bone density but also to estimate fat percentage (165); however, it is also a very expensive method that is not applicable to patients at home. Comparing the DXA with bioelectrical impedance reveals both agreement and disagreement. Agreement between the two methods related to measuring fat mass has been found in some studies (166,167). This agreement is based on normal-weight subjects, and Sun et al. (2005) found a tendency towards over- and underestimation of fat% using bioelectrical impedance in lean and obese subjects, respectively (167). This underestimation in obese subjects is in line with other studies comparing the use of bioelectrical impedance and DXA scanner for measuring fat mass (168,169). This is important to keep in mind, as T2D is often linked to overweight (170). Fat callipers can also be used to measure fat percentage, but several precautions must be considered. First, the use of a fat callipers requires skills to obtain precise measures. Second, fat callipers cannot be applied by the patients themselves; someone else is required to perform the measurement. Third, fat callipers come in a broad variety, and the most reliable fat callipers are quite expensive. Based on these considerations, the Tanita scale was chosen as the method because it is easy to use and can be used by the patients themselves.

Blood pressure

T2D is often associated with high blood pressure, and a high blood pressure is a predictor of cardiovascular complications (171,172). Therefore, it can be useful to monitor blood pressure on a regular basis in patients with T2D. Most patients consult their GP on a regular basis for control of their T2D, and this control includes blood pressure. Measuring blood pressure at the GP or hospital can be biased by the so-called "white coat effect" (173). This is an argument for home-based measuring of BP. Equipment to measure blood pressure is easily accessible, inexpensive and easy to use, and the results are easy to interpret. To ensure reliability and validity of measurements, instructions must be given with respect to standardising the measure. In this matter, placement of the cuff, time of day and level of activity before measuring are among important factors (174). Smoking should also be taken into account, as smoking is related to an acute increase in blood pressure (175).

Blood glucose

Self-monitoring blood glucose (SMBG) is recommended in patients with non-insulin-treated T2D as a part of self-management education according to the International Diabetes Federation (IDF) (176). Incorporating SMBG in regular care can be useful in setting and evaluating treatment goals (176). Furthermore, monitoring can prevent hypoglycaemia, which can be lethal in insulin-dependent diabetes (177). Several methods can be used to monitor blood glucose, glucose control and insulin sensitivity. As the present studies focus on simple methods that can be applied at home, several methods were deselected as they were invasive or too expensive and required special equipment. These methods included HbA_{1c}, venous blood samples and hyperinsulinaemic-euglycaemic clamps. Excluding these methods means compromising on the exactness of the values; still, using the same methods every time makes it possible to compare values. Although OGTT is usually performed in a clinical setting, it is possible to do the test at home. Still, the patients must be educated in using the same dose of glucose every time and in measuring fasting glucose after 10 hours of fasting and the 2h-glucose after sitting still for 2 hours after ingestion.

8.2.4 Interview and analysis of interview

In Study 4, an interview with the patients was completed. This qualitative method was added to incorporate the patients' experiences with using technology-based feedback on a HIT protocol performed at home.

A semi-structured interview was chosen as a method, and it is one of the more secure methods for conducting interviews. A brief description of the different methods is given below:

- A structured interview refers to an interview with pre-established questions with little or no room for variation. All participants receive the same questions, and the interviewer controls the interview (178).
- A semi-structured interview is characterised by an interview guide containing themes and/or questions that need to be answered. Additional questions to clarify an answer are allowed (179,180).
- In an unstructured interview, no or very few questions are planned. The unstructured interview allows questions based on the response of interviewee with the result that very interviews become very diverse. (181).
- A focus-group interview produces data on social groups' interpretations, interactions and norms. A group of participants is placed together with the interviewer as a facilitator, and different topics are discussed (180).

The semi-structured interview was chosen to ensure that the right themes were raised while still allowing additional questions to be asked to clarify the patients' attitudes. Focus-group interview was deselected, as it is not suitable for producing data on the individual's lifeworld which was the aim of the present study (182).

The interviews were analysed using phenomenology as a theoretical approach, which is tantamount to letting the phenomena speak for themselves and leaving out the analyser's pre-understanding (183). Hermeneutics is another approach that could have been taken. In hermeneutics, the interviewer's pre-understanding is incorporated into the processing of the interview. This means that the interviewer interprets the meaning of the interview instead of gathering knowledge about the topic (183). In the present study, the aim of the interview was to get knowledge about the patients' experiences with the use of technology, home training and HIT, which supports the choice of phenomenology as a theoretical approach.

Systematic text condensation (SCT) was used as a method to analyse the interview. This method is inspired by Giorgi´s phenomenological analysis and by grounded theory and has been modified by Kirsti Malterud (180,184). The aim of the phenomenological-inspired analysis is to develop knowledge about the informants' experiences and life worlds within a special field, and it aims at describing instead of analysing and explaining (184). Doing this, the analyser must try to bracket his or her pre-understanding. Doing this completely is impossible, but various methods may be recruited to diminish the influence of such pre-understanding; e.g. realising that the pre-understanding exists and exploring what is consists of (180). In the present study, this was specifically done by thoroughly determining which answer the analyser would expect from each question and thereby clarifying any pre-understanding. This process is important to eliminate any pre-understandings and focus on the patients being interviewed (180).

8.3. Reliability and validity

The findings presented in this PhD thesis arise from studies that included a limited number of patients. Reflections regarding the transferability of the findings to other but similar diabetic patients in similar settings are thus required.

To ensure external validity, internal validity is a precondition. However, the studies did not focus on examining the validity of the instruments used; instead, we relied on using instruments that are highly acclaimed and thus accepted for wide use.

In terms of reliability, several precautions were made to ensure this. First, internal consistency was measured in the pilot test in Study 3 using Cronbach's alpha coefficient which is the most commonly used method to measure internal consistency where questions have two or more possible responses (185). Second, stability was important, and we therefore used the same instrument for the same participant for all measures and calibrated the instruments before use if possible. Third, the same person conducted all the measures and followed a strict protocol.

Overall, the stringency of the protocol and the measurements, the choice of instruments used as well as the precautions taken in interpreting the findings heighten the internal validity and reliability of the studies in this PhD thesis.

9. Conclusions and perspectives

This PhD project describes the preliminary work of developing a concept aiming at engaging more patients with T2D in physical activity and training. Until now, the offer made to patients with T2D is a referral to Sundhedscenter Aalborg from the GP for an 11-week rehabilitation period focusing on patient education, training and diet. After 11 weeks, the patients are more or less left on their own, which increases the risk that they do not maintain training. Using technology-based feedback, the health professionals can continue to monitor patients after they have returned to their normal setting. Using measurements of T2D-related parameters, e.g. blood glucose, blood pressure, etc., the supervision can both focus on the training, the medical status and its benefits. As patients with T2D often state lack of time as their reason for not engaging in regular physical activity, the training approach in this study focused on time-saving HIT. The conclusions from this PhD project are:

- It appears to be possible to measure training-induced progress on T2D-related physical parameters
- It appears to be possible for patients to reach the right intensity and frequency of training with the use of technology to monitor training and give feedback.
- The patients included in this PhD project had an adequate level of health literacy and a positive attitude towards diabetes, which furthers high adherence

Further research must be conducted before the concept is ready to be implied in municipalities by health professionals (e.g. physiotherapists). This research should involve:

- Larger-scale studies to confirm the expediency of using simple methods to monitor training progress
- Further validation of DAS including health professionals, patients with T1D and a larger sample size including T2D.
- Longer-term studies to study if adherence to home-training is persistent.
- Connecting the use of simple methods with the technology-based supervision of home-training.
- Developing an app containing both training features, the ability to note the progress in T2D-related parameters and extended possibilities for supervision including “Q&A” between the patient and the health care professional.

9. Conclusion and perspectives

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